REMARKS

Claims 1-26, 33-40 and 61-74 are pending in the application. Claims 1-26, 33-36, 38-40, 61-69, and 71-73 are withdrawn from consideration. Claims 37 and 74 are currently amended to better clarify what applicants believe to be the invention. New claims 75-80 have been added for consideration. Support for the claim amendments can be found throughout the current specification, figures and claims as filed, and in the specification, figures and claims of the priority applications, as noted below.

In USSN 09/734,221, filed Dec. 11, 2000	On page 8, lines 29-32; on page 9, lines 12-21; in Example 1 on page 49, lines 29-33, continuing on to page 50, lines 1-9; in Example 2 on page 50, lines 11-30; in Example 4, page 53, lines 10-34, continuing on to page 54, lines 1-3; in Figures 3a and 3b described on page 15, lines 8-25; in Figure 4 on page 15, lines 27-31 and in original claims 41, 43, 44, 45, 46, 48, 49 and 50.
In USSN 08/861,105, filed May 21, 1997	On page 8, lines 29-32; on page 9, lines 12-21; in Example 1 on page 49, lines 29-33, continuing on to page 50, lines 1-9; in Example 2 on page 50, lines 11-30; in Example 4, page 53, lines 10-34, continuing on to page 54, lines 1-3; in Figures 3a and 3b described on page 15, lines 8-25; in Figure 4 on page 15, lines 27-31 and in original claims 41, 43, 44, 45, 46, 48, 49 and 50.
In USSN 08/858,660, filed May 19, 1997	On page 9, second paragraph; in Example 1 on page 49, second paragraph entitled "CC-CKR-5 promotes env-mediated fusion"; in Example 2 on page 50, third paragraph continuing on to page 51, first paragraph; in Example 4, page 52, third paragraph to page 53, first and second paragraph; Figures 3a and 3b, described on page 14, third paragraph to page 15, first paragraph; Figure 4, page 15, second paragraph; and in claims 41, 43, 44, 45, 46, 48, 49 and 50.
In USSN 60/017,157, filed May 20, 1996	In Example 1 on page 20, first paragraph entitled "CC-CKR-5 promotes env-mediated fusion"; in Example 2 on page 20, second paragraph continuing on to page 21, first paragraph; in Figures 3a and 3b, described on page 11, third paragraph, continuing on to page 12 through page 13, first paragraph; Figure 4, described on page 13, second paragraph; and in claims 23, 24, 26 and 27.

No issue of new matter is believed to be introduced by this amendment. Reconsideration of this application is respectfully requested.

Applicants' representatives would like to express their sincere appreciation for the courteous and constructive telephonic interview held with Examiners Bao Li and James Housel

on February 28, 2006 as related to the claims under consideration. As noted in that conversation, the Examiners have kindly agreed to consider claim amendments directed to clarification of the fusion methods used in step b) of claim 37 and 74 to better differentiate the present invention from the references noted by the Examiners. Accordingly, claims 37 and 74 have been amended to recite the methods of measuring the fusion event (or inhibition thereof), between a target cell containing both CD4 and CCR5 and a macrophage-tropic HIV virus or a virus pseudotyped with a macrophage-tropic HIV envelope, as suggested by the Examiners, and is provided herein for the Examiner's consideration.

Rejection under 35 U.S.C. §112, first paragraph

The Examiner has rejected claims 37, 70 and 74 for non-compliance with the enablement requirement under 35 U.S.C. 112, first paragraph. More particularly, the Examiner alleges that while the specification is enabling for a method of screening an HIV-1 macrophage tropic (HIV M-tropic) fusion inhibitor with cells expressing both CD4 and CCR5 in the presence of an M-tropic HIV-1 infection or a virus pseudo-typed with a full-length HIV M-tropic envelope protein, it does not reasonably provide enablement for a method of screening any or all HIV fusion inhibitors with a cell that only expresses CCR5 in the presence of any or all kinds of virus pseudotyped with any or all kinds of M-tropic envelope, wherein an inhibitor identified by the method can be used for prevention of AIDS. The Examiner alleges that the specification does not enable a person skilled in the art to make or use the invention commensurate in scope with the claims, as currently pending. Moreover, the state of the art does not teach that any macrophage-tropic envelope protein can bind to CCR5 and induce fusion as the Examiner had pointed out in the previous office action mailed on December 21, 2004. The Examiner has noted several references that support the infection of human macrophages by Dengue virus via the binding of the envelope protein to target cells. However, the infection of cells by Dengue virus is not mediated by CCR5. The Examiner notes that the specification does not provide evidence to support the breadth of the claims.

Applicants respectfully traverse the Examiner's rejection and have amended claims 37 and 74 to recite that the target cells express both CD4 and CCR5 and that the virus is a macrophage-tropic HIV virus or that the virus is pseudotyped with a macrophage-tropic HIV envelope. For example, claim 37 now reads:

"A method of identifying an agent that inhibits entry of a macrophage-tropic HIV virus into a target cell, wherein entry of the macrophage-tropic HIV virus to said target cell is a fusion process mediated by CCR5 and CD4 expressed on the surface of said target cell, the method comprising the steps of:

(a) contacting said cell with a macrophage-tropic HIV virus or a virus pseudotyped with a macrophage-tropic HIV envelope in the presence or absence of said agent;

(b) measuring the fusion between the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic HIV envelope and said target cell; wherein fusion is measured by a method selected from the group consisting of visual (microscopic) assessment of syncytia formation, measurement of reporter gene expression and measurement by fluorescence activated cell sorting (FACS), and

(c) determining whether fusion of the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic HIV envelope is inhibited in the presence of the agent but not in the absence of the agent."

Claim 74 has been amended in a similar manner, and it now reads:

"A method of identifying an agent that inhibits entry of a macrophage-tropic HIV virus into a target cell, wherein entry of the macrophage-tropic HIV virus into said target cell is a fusion process mediated by CCR5 and CD4 expressed on the surface of said target cell, the method comprising the steps of:

(a) contacting said cell with a macrophage-tropic HIV virus or a virus pseudotyped with a macrophage-tropic HIV envelope in the presence or absence of said agent;

(b) measuring the fusion between ~~to~~ the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic HIV envelope and said target cell, wherein fusion is measured by a method selected from the group consisting of visual (microscopic) assessment of syncytia formation, measurement of reporter gene expression and measurement of fluorescence activated cell sorting (FACS); and

(c) determining whether fusion of the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic HIV envelope is inhibited in the presence of the agent but not in the absence of the agent;

(d) contacting the agent with CCR5; and

(e) determining if the agent binds to CCR5; wherein an agent that binds CCR5 is selected; and wherein steps (d) and (e) can be performed either prior to or after steps (a)-(c)."

In light of the foregoing amendment, withdrawal of the rejection of claims 37, 70 and 74 under 35 U.S.C. 112, first paragraph, is respectfully requested.

Rejection under 35 U.S.C. §102

The Examiner has maintained her rejection of claim 37 under 35 U.S.C. 102(a) as being anticipated by Cocchi, *et al.* (Science 1995, Vol. 270, pp. 1811-1815) , in light of Moriuchi et al. (J. Immunol. 1997, Vol. 159, pp. 5441-5449) for the reasons cited in the previous Office Action.

The Examiner's Position

More particularly, the Examiner alleges that the method disclosed by Cocchi et al. teach methods using the same type of cell that expresses CCR5, the same kind of virus, and the same step of putting a test reagent into the test system comprising both macrophage-tropic HIV-1 virus and a target cell that expresses CD4 and CCR5. The Examiner further alleges that because the CC chemokines disclosed by Cocchi et al. competitively bind CCR5 with the macrophage-tropic HIV envelope protein, and consequently inhibit said virus infection via inhibiting the fusion process regardless of whether the CCR5 was known as an M-tropic HIV co-receptor at the time of the Cocchi et al. paper. The Examiner apparently offers Moriuchi et al. for the teaching of a CCR5 receptor.

Applicants' Position

Applicants respectfully traverse the rejection and have amended claim 37 to recite specific methods for measuring the fusion of the macrophage-tropic HIV virus or virus

pseudotyped with a macrophage-tropic HIV envelope to a target cell in the presence or absence of a test agent.

Applicants respectfully point out to the Examiner that Cocchi et al. do not teach or suggest all of the limitations of claim 37 as currently amended, either expressly or inherently. The Examiner previously acknowledged that ***Cocchi et al. do not teach or suggest*** a method of identifying an agent that inhibits entry of a macrophage-tropic HIV virus into a target cell, ***wherein entry of the macrophage-tropic virus into cells is a fusion process mediated by CCR5 and CD4 expressed on the surface of the target cell***, the method comprising contacting the agent with a cell in the presence of the macrophage-tropic virus and monitoring whether the virus fuses with the cell in the absence of the agent but does not fuse with the cell in the presence of the agent. Moreover, the claim has been amended to recite the methods taught by the present application for measuring fusion of the virus to the target cell, which was suggested by Examiner Housel in a telephonic interview held on February 28, 2006, as a means of differentiating from Cocchi et al.. Furthermore, ***Cocchi et al. do not teach or suggest that chemokines such as RANTES, MIP-1 alpha or MIP-1 beta prevent the virus from entering the cell via a fusion mechanism***, as recited by the methods in the currently amended claims. As noted previously, Cocchi et al. clearly believed that the chemokines exerted their effect ***subsequent*** to viral fusion to the cell. Moreover, as noted previously, Cocchi et al specifically state on page 1814 in the middle column, second paragraph:

> *"Chemokine-mediated control of HIV may occur either directly, through their inherent anti-lentiretroviral activity, or indirectly, through their ability to chemoattract T cells and monocytes in proximity of the infection loci."*

Cocchi et al. **do not teach or suggest** the fact that the chemokines **prevent <u>fusion</u> of the virus to the cell membrane, as measured by the methods as currently claimed**. The fact that Cocchi et al. teach inhibition of viral replication is not equivalent to the teachings of the present invention. Applicants assert that there are many other means by which a compound/chemokine may prevent viral replication, including events that are post fusion and post entry of the virus into the cell. In fact, Cocchi et al. **do not teach or suggest** the methods of inhibition of viral fusion with the cell membrane using the chemokines. It was only at the time of the present invention that such knowledge became available.

Furthermore, as also noted previously, at the time the Cocchi et al. reference was published, the CCR5 receptor had not yet been identified, nor had its role as a co-factor with CD4 for viral fusion with cells been elucidated. Therefore, given the lack of knowledge at the time of publication of the Cocchi et al. reference of the very existence of the CCR5 receptor, it certainly cannot be that one of skill in the art would recognize that this element of the invention as claimed was present in the teachings of Cocchi et al. Moreover, based upon the teachings of Cocchi et al., Applicants assert that **there would have been no motivation to screen for agents using the methods as currently claimed for measuring fusion of the HIV macrophage-tropic strains of virus or macrophage tropic viruses pseudotyped with an HIV envelope protein, to cells expressing both CD4 and CCR5, since the role of CCR5 as a co-receptor with CD4, which allowed fusion of the virus to the cell was not known at that time. Cocchi et al. clearly do not teach or suggest that the chemokines block viral fusion with the cell membrane using the methods as currently claimed. It is Applicants' position that Cocchi et al. teach that inhibition of viral replication by the chemokines occurs subsequent to viral fusion, and as such, they do not teach the methods of the present invention, as currently claimed, that is, that the chemokines act to prevent viral "fusion" to the cell membrane using the fusion assays as described in the current application and as currently claimed.**

As such, claim 37 has been amended as follows:

"*A method of identifying an agent that inhibits entry of a macrophage-tropic HIV virus into a target cell,* ***wherein entry of the macrophage-tropic HIV virus to said target cell is a fusion process mediated by CCR5 and CD4*** *expressed on the surface of said target cell, the method comprising the steps of:*

(a) contacting said cell with a macrophage-tropic HIV virus or a virus pseudotyped with a macrophage-tropic HIV envelope in the presence or absence of said agent;

(b) measuring the fusion between the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic HIV envelope and said target cell; wherein fusion is measured by a method selected from the group consisting of visual (microscopic) assessment of syncytia formation, measurement of reporter gene expression and measurement by fluorescence activated cell sorting (FACS), and

(c) determining whether fusion of the macrophage-tropic HIV virus or the virus pseudotyped with a macrophage-tropic HIV envelope is inhibited in the presence of the agent but not in the absence of the agent."

Applicants assert that Cocchi et al. do not teach or suggest a method of identifying an agent that inhibits entry of a macrophage-tropic HIV virus into a target cell, wherein entry of the macrophage-tropic HIV virus into said target cell is a fusion process mediated by CCR5 and CD4 expressed on the surface of said target cell, and wherein one of the steps of the method recites how fusion is measured eg. by a method selected from visual (microscopic assessment of syncytia formation, or reporter gene expression and measurement by fluorescence activated cell sorting, as demonstrated in the present invention in Examples 1 on page 49-50 and in Example 4 on page 53-54.

In light of the foregoing claim amendments, Applicants respectfully request withdrawal of the rejection.

Fees

A check in the amount of $150.00 to cover additional claim fees is enclosed. No other fees are believed to be necessitated by the foregoing Response. However, should this be erroneous, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or credit any overages.

Conclusions

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,

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